

## Research Article

# Transcriptional Regulation of $\Delta 6$ -Desaturase by Peroxisome Proliferative-Activated Receptor $\delta$ Agonist in Human Pancreatic Cancer Cells: Role of MEK/ERK1/2 Pathway

Maryam Darabi,<sup>1</sup> Shima Byagowi,<sup>2</sup> Shabnam Fayezi,<sup>1,3</sup> Masoud Darabi,<sup>1</sup> Shahab Mirshahvaladi,<sup>4</sup> and Mehdi Sahmani<sup>2</sup>

<sup>1</sup> Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz 5165665811, Iran

<sup>2</sup> Department of Clinical Biochemistry and Genetics, Cellular and Molecular Research Center, Faculty of Medicine, Qazvin University of Medical Sciences, Qazvin 3411975981, Iran

<sup>3</sup> Department of Anatomy and Cell Biology, Shahid Beheshti University of Medical Sciences, Tehran 193954719, Iran

<sup>4</sup> Department of Biotechnology, Cellular and Molecular and Burns Research Centers, Iran University of Medical Sciences, Tehran 141556183, Iran

Correspondence should be addressed to Mehdi Sahmani; [m.sahmani@gmail.com](mailto:m.sahmani@gmail.com)

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The  $\Delta 6$ -desaturase ( $\Delta 6D$ ), also known as fatty acid desaturase 2, is a regulatory enzyme in *de novo* fatty acid synthesis, which has been linked to obesity and diabetes. The aim of the present study was to investigate the effect of peroxisome proliferative-activated receptor  $\delta$  (PPAR $\delta$ ) agonist and MEK/ERK1/2-dependent pathway on the expression of  $\Delta 6D$  in human pancreatic carcinoma cell line PANC-1. PANC-1 cells cultured in RPMI-1640 were exposed to the commonly used ERK1/2 pathway inhibitor PD98059 and PPAR $\delta$  agonist GW0742. Changes in mRNA and protein expression of  $\Delta 6D$  were then determined using real-time RT-PCR and Western blot, respectively. The expression of  $\Delta 6D$  ( $P < 0.01$ ) increased following treatment with PPAR $\delta$  agonist both at mRNA and protein levels, whereas no significant change was observed after treatment with MEK/ERK1/2 pathway inhibitor. It was also found that the increase in the expression of  $\Delta 6D$  in response to GW0742 was significantly inhibited by PD98059 ( $>40\%$ ,  $P < 0.05$ ) or EGF receptor-selective inhibitor AG1478 ( $>25\%$ ,  $P < 0.05$ ) pretreatment. PPAR $\delta$  and MEK/ERK1/2 signaling pathways affect differentially the expression of  $\Delta 6D$  in pancreatic cancer cells. Furthermore, there may be an inhibitory crosstalk between these two regulatory pathways on the mRNA expression of  $\Delta 6D$  and subsequently on  $\Delta 6D$  protein expression.

## 1. Introduction

Numerous *in vitro* and *in vivo* studies indicate the critical role of fatty acids in cell membrane fluidity, which in turn affect ligand binding and cellular signal transduction of surface receptors and G-proteins [1–3]. This role has been demonstrated by the fact that the altered levels of fatty acid desaturase enzymes are associated with various human diseases like diabetes and atherosclerosis [4, 5]. Studies have shown that lipotoxicity of human pancreatic islets, which is attributed to accumulation of saturated fatty acids, is one of the important causes of dysregulated insulin secretion and

apoptosis of pancreatic  $\beta$ -cell [6, 7]. In contrast to saturated fatty acids, unsaturated fatty acids play a key role in survival of the pancreatic  $\beta$ -cell [8, 9]. The membrane-bound enzyme  $\Delta 6$  fatty acid desaturase ( $\Delta 6D$ ), encoded by the *fatty acid desaturase 2* (*FADS2*) gene, is the first and rate-limiting enzyme in the synthesis of unsaturated fatty acids. *FADS2*-deficient mouse model has revealed that  $\Delta 6D$  is the main enzyme in *in vivo* production of n-6 polyunsaturated fatty acids (PUFA) [10].

The delta isoform of the peroxisome proliferator-activated receptor (PPAR)  $\delta$  is a family of nuclear receptors regulating the expression of genes involved in fatty acid